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EXAMINER
BALLARD, KIMBERLY A

ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/612,665	NIELSEN ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *1-53 and 59-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. Claims 1-68 are pending in the instant application.

Election/Restrictions

2. Applicant's election of group IV, claims 54-56, in the reply filed on December 20, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant further notes that they have amended claims 57 and 58 from use claims to method claims, and therefore assert that the newly amended claims should be contained within group IV. Accordingly, claims 57-58 are hereby included in group IV.

3. The following species elections, which read upon the elected claims of group IV, have been elected by the Applicant: SEQ ID NO: 62 for the tissue protective cytokine (readable upon claims 54-58), ganglion as the species of cell (readable upon claims 54-58), neuronal as the distinct species of cell (readable upon claims 54-58), increasing hematocrit as the species of activity (readable upon claims 56-58), and retinal ischemia as the species of injury (readable upon claims 57-58), all elected with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement or in the species election requirement, all elections have been treated as an election without traverse (MPEP § 818.03(a)).

4. Upon further consideration, the species election requirements set forth in paragraphs 4, 6, 7, 9 and 10 of the previous office action (the 06/20/2006 restriction requirement), with regard to: distinct species of cell (¶ 4), endothelial cell barrier (¶ 6), distinct species of cell (¶ 7), the activity lacking from the instant cytokine of the claimed invention (¶ 9), and the cause of tissue injury (¶ 10), are hereby withdrawn. However, the restriction requirement between groups I-VII and the additional species election requirements are **maintained**.

5. Claims 1-53 and 59-68 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 20, 2006.

6. Claims **54-58**, to the extent they read upon the elected species of SEQ ID NO: 62, are under examination in the instant office action.

Information Disclosure Statement

7. A signed and initialed copy of the IDS paper submitted 10/20/2004 is enclosed in this action.

Claim Objections

8. Claims 56-58 are objected to because of the following informalities: The claims recite non-elected subject matter. Additionally, claims 56-57 recite dependency from non-elected claims 1-6. Appropriate correction is required.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claim 57 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,531,121 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '121 patent contains claims directed to methods for protecting or maintaining the viability of an erythropoietin-responsive cell, tissue or organ in a human being comprising administering an amount of human asialoerythropoietin

effective to translocate an endothelial cell barrier and protect or maintain said viability of said cell, tissue or organs, which would encompass the instantly claimed method of protecting against tissue injury. The '121 patent also discloses that asialoerythropoietin lacks activities normally associated with EPO, which would address the negative limitation of instant claim 57 regarding the activities that the recombinant tissue protective cytokine lacks. Additionally, claims 1-10 of the '121 patent recite the protection or maintenance of erythropoietin-responsive cells, tissues or organs, including CNS cells or tissue, retinal cells or tissue, spinal cord cells or tissue, or heart cells or tissue, which are species that would anticipated the instantly claimed tissue of claim 57. Accordingly, the '121 patent renders obvious instant claim 57.

11. Claims 54-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35 and 37-38 of copending Application No. 10/188,905. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '905 application contains claims to a method for protecting, maintain or enhancing the viability of a cell, tissue or organ isolated from a human body comprising exposing said cell, tissue or organ to a pharmaceutical composition (such as in claim 35) comprising a modified erythropoietin molecule that lacks at least one erythropoietic activity (claim 35), which would anticipate the genera of mammalian body and mutein recombinant tissue protective cytokine instantly claimed. Further, the '905 application recites the use of pharmaceutical compositions comprising the modified erythropoietin molecule lacking specific

erythropoietic activities for the protection against and prevention of a tissue injury as well as the restoration of and rejuvenation of tissue and tissue function in a mammal (claim 37), wherein the injury is caused by retinal ischemia among many other things (claim 38). Accordingly, the '905 application renders obvious instant claims 54-58.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 57-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 15 of copending Application No. 09/716,960. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods in the '960 application recite protection of an excitable tissue in a mammal having a neurodegenerative disease (claim 1) or having mechanical trauma, diabetic neuropathy or amyotrophic lateral sclerosis (claim 15), which are species recited in instant claim 58 and which would render obvious the genus of tissue injury of instant claim 57. Further, the claims of the '960 application recite administration of EPO, wherein the administering does not increase the hematocrit in said mammal, which again would render obvious the recombinant tissue protective cytokine lacking at least one activity, such as increasing hematocrit, of instant claim 57. Accordingly, the '960 application renders obvious instant claims 57-58.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 54-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2 and 5 of copending Application No. 10/351,640. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '640 application contains claims directed to a method for protecting or maintaining the viability or function of an isolated mammalian cell, tissue, organ or body part that would render obvious the instant claims. For example, claim 2 of the '640 application recites administration of asialoerythropoietin to protect said cells, tissues, organ or body part isolated from a mammalian body (claim 5), wherein asialoerythropoietin (asialoEPO) is disclosed to lack activities normally associated with erythropoietin (EPO), such as effecting bone marrow by increasing hematocrit, etc. Thus, asialoEPO is a species which would render obvious the claimed mutein recombinant tissue protein cytokine of instant claims 54-56.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claim 57 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/185,841. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '841 application contains a method directed to protecting, maintaining, enhancing or restoring the function or viability of erythropoietin-

responsive mammalian cells, tissues and organs comprising administering to a mammal a pharmaceutical composition comprising a chemically modified erythropoietin, without causing an increase in hemoglobin concentration or hematocrit in said mammal, wherein the chemically-modified erythropoietin is a species that would render obvious the instantly claimed tissue protective cytokine. Accordingly, the '841 application would render obvious instant claim 57.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claim 57 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 4 of copending Application No. 10/573,905. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '905 application contain claims directed to treating, preventing, delaying the onset of, or reducing the effects of proinflammatory cytokines in a mammal, wherein treatment or reduction of proinflammatory cytokines is a mechanistic species that would anticipate the genus of treating or reducing tissue injury. Additionally, claim 4 of the '905 application recites that the chemically modified erythropoietin lacks erythropoietin's erythropoietic effects, which would render obvious the instantly claimed tissue protective cytokine of claim 57.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, first paragraph

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 54-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting, maintaining or enhancing the viability of an erythropoietin-responsive cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a tissue protective cytokine comprising SEQ ID NO: 62, or a method for protecting erythropoietin-responsive tissues against tissue injury due to ischemia/neuroinflammation or restoration of tissue function following tissue injury due to ischemia/neuroinflammation in a mammal comprising administering to the mammal a tissue protective cytokine comprising SEQ ID NO: 62, does not reasonably provide enablement for a method for protecting, maintaining or enhancing the viability of any cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising any mutein recombinant tissue protective cytokine as broadly claimed, or a method for protecting against any tissue injury as broadly claimed; prevention of tissue injury; restoring tissue and tissue function in a mammal; or rejuvenating tissue and tissue function in a mammal comprising administering any mutein recombinant tissue protective cytokine as broadly claimed. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claims 54-56 are drawn to an *ex vivo* method of protecting, maintaining or enhancing the viability of isolated mammalian cells, tissues or organs, comprising exposing said tissue to a pharmaceutical composition comprising a tissue protective cytokine that lacks at least one activity normally associated with erythropoietin. Claims 57-58 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, restoration of tissue and tissue function, or regeneration of tissue and tissue function in a mammal comprising administering to the mammal a tissue protective cytokine that lacks at least one activity normally associated with erythropoietin. A number of causes of the injury are recited (as in claim 58), ranging from acute causes such as stroke, ischemia, myocardial infarction, radiation damage and inflammation, to much more complicated and/or chronic causes such as multiple sclerosis, seizure disorder, neurodegenerative disease (including, for example, Alzheimer's disease, Parkinson's disease, ALS, Creutzfeldt-Jakob disease), AIDS dementia, mood and

anxiety disorder, alcoholism, and even aging (age-related loss of cognitive function), cerebral palsy and autism to name a few.

The nature of the invention is the demonstration that the administration of or exposure of cells to erythropoietin (EPO) – or a particular recombinant erythropoietin such as the variants K45D, R103E, R150E, S100E, and S100e/K45D – is capable of protecting cells and tissues from tissue injury, such as ischemia or reperfusion injury, as may occur during organ transplant or stroke, for example. The instant specification demonstrates, though is not limited to, the following pertinent examples: recombinant EPO variants – the muteins K45D and S100E – provided neuroprotection to SK-N-SH neuroblastoma cells in culture (Example 3); EPO can cross the blood-brain barrier (Example 2) and the blood-eye barrier (Example 9); treatment with S100E enhances the viability of PC12 cells subjected to NGF withdrawal in culture (Example 16); the variants S100E, R103E and R150E each have several times to several orders of magnitude lower potency than EPO in an UT-7 cell bioassay, whereas the K45D variant demonstrated a potency equivalent to EPO (UT-7 is a leukemia EPO-dependent cell line used for the determination of the erythroid effect of recombinant tissue protective cytokines) (Example 17); and finally, treatment with R103E, R150E, S100E or S100e/K45D in rats subjected to retinal ischemia resulted in reducing injury (measured by comparative electroretinograms of peak amplitude latency in the injured and uninjured eyes) compared to saline treated rats and was equal or better than EPO-treated rats (Example 18).

The state of the art recognizes the neuroprotective effects of EPO in animals administered EPO, see Brines et al. (2000) *Proc Natl Acad Sci USA*, 97(19): 10526-10531, listed on Applicant's IDS. The art also recognizes that the *in vitro* and *in vivo* ischemic injury models employed in the instant disclosure are associated either directly or indirectly with inflammation, immune-mediated inflammatory responses, or apoptosis (see, for example, Brines et al. at p. 10531 and Rosenbaum et al. (1997) *Vision Res.* 37(24): 3445-3451). Applicant's invention is predicated on similar findings, that is, that EPO has a neuroprotective effect as well as being able to reduce retinal ischemic damage. Applicant extrapolates these findings into a method for protecting, maintaining or enhancing the viability of any isolated cell, tissue or organ or a method of protecting against and preventing any tissue injury in any tissue in a mammal. The art recognizes that only certain cells and tissues express erythropoietin receptors, such as neurons, hematopoietic cells, kidneys, heart tissue, and adrenal cortex and medulla (see, for example, Juul et al. (1998) *Pediatr. Res*, 43: 40-49, and Westenfelder et al. (1999) *Kidney Intl.* 55: 808-820; both listed on Applicant's IDS). As not all cells, tissues or organs possess EPO receptors and thus would not be considered "erythropoietin-responsive", it is unclear how such cells and tissues would be protected, maintained or enhanced viably, etc. by the tissue protective cytokine. Accordingly, it would appear that Applicant provides limited findings – mainly related to the neuroprotective effects of EPO – and then presents an invitation to experiment to determine which other cells, tissues or organs would be protected from what other tissue injuries.

Moreover, claims 54-58 are broadly directed to methods involving the use of any mutein recombinant tissue protective cytokine that is defined only by negative functional limitations (such as in claims 56-58) and with no structural limitations. Moreover, claims 57-58 are broadly directed to methods for the prevention of any tissue injury or the restoration and/or regeneration of tissue or tissue function. Note that with regard to the claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of claims 54-55 is an ex vivo method encompassing the use of any mutein recombinant tissue protective cytokine, and claim 56 is directed to an ex vivo method encompassing the use of any recombinant tissue protective cytokine lacking at least one particular activity normally associated with erythropoietin. The broadest reasonable interpretation of claims 57-58 is of a method of protecting against or preventing any tissue injury *in vivo*, or a method of restoring or regenerating new tissue or tissue function *in vivo*, using any recombinant tissue protective cytokine so long as it lacks at least one commonly associated erythropoietic activity.

While the skill level in the art is high, the level of predictability is low. The working examples provided in the instant specification are limited to demonstrating: 1) the ability of EPO to cross endothelial cell barriers, 2) the effectiveness of EPO, specific

variant EPO species, and/or specific chemically modified EPO species to reduce tissue injury associated with transplantation, reperfusion/ischemia, or apoptosis, 3) the ability of EPO to reduce inflammation associated with injury, and 4) the ability of EPO to improve tissue function following injury and/or reduce the negative consequences of injury on particular cognitive or motor functions. The instant specification, however, does not provide sufficient guidance or evidence that the claimed method can protect against *any* tissue injury or restore tissue lost to injury or rejuvenate tissue or tissue function, which would require evidence of *de novo* tissue synthesis. For example, there is no evidence presented that EPO could protect against tissue injury caused by a thermal or chemical burn, such as might occur to the skin. Moreover, the sparing of neuronal tissue mass lost to injury indicates only that EPO is capable of reducing inflammation-associated neuronal cell death, such as apoptosis or necrosis, but does not go so far as to implicate EPO as being able to induce new cellular growth, which would be necessary to restore or rejuvenate tissue or tissue function. Similarly, the art recognizes that EPO administration is able to reduce the extent of neuronal tissue damage following insult or injury, but EPO does not in fact cause the production, synthesis, or rejuvenation of new tissues (see Brines et al. (2000)). Thus the scope of the claimed invention is not commensurate with the teachings of the instant specification or with teachings in the prior art. Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the claimed

tissue protective cytokine molecule – or any EPO molecule for that matter – is able to completely prevent tissue injury.

Additionally, as discussed above, the subject matter broadly encompasses treatment of diverse neurological ailments ranging from neurodegenerative diseases such as Alzheimer's disease, Creutzfeldt-Jakob disease, ALS and Parkinson's disease, to conditions such as memory loss, age-related cognitive decline, anxiety and mood disorders, to inherited diseases such as Leigh's disease, to diseases of unknown or uncertain etiology such as autism, cerebral palsy and alcoholism, and many other diseases, disorders and conditions. The instant specification fails to provide any evidence or sound scientific reasoning to support a conclusion that the working examples, which pertain to the reduction of tissue injury, inflammation or apoptosis associated with injury, could be successfully extrapolated to methods of treating injury caused by multifaceted neurodegenerative or neurological diseases or conditions such as those listed above and in claim 58. The only examples provided in the instant specification pertain to treatment of acute tissue injury or acute tissue stress/ischemia. However, all of the neurodegenerative diseases and most of the neurological conditions and disorders recited in instant claim 58 are known to be chronic in nature and have complicated pathologies and etiologies. Moreover, neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's disease have proven recalcitrant to treatment in the art, even when treatment involves the use of anti-inflammatory or anti-oxidant agents (see for example, Steece-Collier et al. *Proc Natl Acad Sci USA*, 2002; 99(22): 13972-13974; Diaz Brinton & Yamazaki, *Pharmaceutical Res*, 1998; 15(3): 386-

398; Feigin & Zgalijardic, *Curr Opin Neuro*l, 2002; 15: 483-489). One would have no basis for concluding that administration of any tissue protective cytokine, even the particular variant EPO species disclosed in Example 18 of the instant specification, would have any effect on protecting tissue injury in any or all these chronic degenerative conditions because such assertion is not supported by any factual evidence of record. Hence, it would require undue experimentation on the part of a skilled practitioner to discover how to practice the full scope of the instant invention, as currently claimed.

Additionally, the scope of the claims includes the use of mutein recombinant cytokines or recombinant cytokine molecules that are defined only by negative limitations and broad functional limitations, such as "tissue protective". For example, the instant specification broadly defines "mutein" or "variant protein" as "a protein comprising a mutant amino acid sequence and includes polypeptides which differ from the amino acid sequence of native erythropoietin due to amino acid deletions, substitutions, or both" (p. 4, lines 1-4). However, it is also known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function or structure. For example, WO 94/24160 document by Boissel et al. (published October 27, 1994) note that replacement of particular residues, such as Lys140, Arg143, Ser146, Asn147 or Lys154, with alanine resulted in an EPO molecule with significantly increased (3-fold) biological activity, whereas replacement of a tyrosine residue (Tyr156) with alanine resulted in a molecule with slightly decreased biological activity (see p. 69, lines 2-11, and Figures 19-22). Boissel et al. additionally note that while an EPO molecule lacking N-linked

carbohydrates may have full *in vitro* biological activity, it has drastically shortened half-life *in vivo* (see p. 40, lines 8-16), and thus would not be predicted to be capable of therapeutic use. The art thus recognizes unpredictability in the biological activity of modified EPO molecules according to recited modifications encompassed by the instant invention in that certain modifications, such as substitution of particular amino acid residues, result in EPO molecules with enhanced biologically activity rather than the desired decreased or deficient biological activity. It would thus appear that certain mutein recombinant cytokine molecules would be potentially inoperative as they are currently broadly recited, requiring undue experimentation of the skilled artisan to determine which particular recombinant molecules retain the desired tissue protective ability and are thus suitable for practicing the claimed methods.

Therefore, in view of the breadth of the claims encompassing the use of molecules with no precise structural requirements, the lack of adequate guidance or working example(s) or data or evidence supporting a therapeutic effect of EPO molecules on the broadly claimed chronic and/or degenerative diseases or disorders, or guidance on their use, the unpredictability in the art of treatment of chronic and neurodegenerative disease, the unpredictability in the art of biological effects of modifying EPO molecules, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

18. Claims 54-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. (Written description guidelines, Federal Register, vol. 66, no. 4, January 2002, 9.1106, column 2).

The claims are directed to *ex vivo* and *in vivo* treatment methods involving exposing an isolated cell, tissue or organ to, or administering to a mammal, a tissue protective cytokine that lacks at least one biological activity normally associated with erythropoietin. Because the methods require the use of cytokine molecules that are defined only by broad functional limitations, the claims encompass a method of using a genus of cytokine molecules.

A description of a genus may be achieved by means of a recitation of a representative number of members, defined by structure and/or function, falling within the scope of the genus, or of a recitation of structural and/or functional features common to the genus, which features constitute a substantial portion of the genus. Applicant has disclosed several mutein EPO molecules – R103E, R150E, S100E (SEQ

ID NO: 62), and K45D – that were shown to have: reduced potency of erythropoietic effects (Example 17), the ability to protect retinal cells from retinal ischemic injury (Example 18), and the capacity of S100E to enhance the viability of cultured neuroblastoma cells subjected to apoptosis (Example 16). However, the scope of the claims encompasses cytokine molecules that are not limited to the elected species, SEQ ID NO: 62 (S100E variant), or to the particular species of Examples 17 and 18. For example, the instant specification discloses that the mutein proteins molecules may be modified by deletion, substitution or both of any amino acid(s) relative to the amino acid sequence of native erythropoietin (p. 4, lines 1-4). The scope of the claims therefore broadly encompasses any number or modified EPO molecules which are defined only in that they are tissue protective and also lack a particular biological activity normally associated with EPO, such as increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity, or increasing thrombocyte production.

Thus, the scope of the claims includes numerous structurally different amino acid molecules, and the genus is highly variable because a significant degree of structural variation is permitted. Structural features that could distinguish the instantly claimed modified erythropoietin molecules in the genus from other molecules in the amino acid class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, there is no means by which the artisan, given any of these cytokine molecules, would know whether it was a member of the genus that could be

used in the claimed methods. The instant disclosure of the several specific mutein EPO species does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of molecules.

Claim Rejections - 35 USC § 112, second paragraph

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "wherein the protection does not effect bone marrow" in claim 55 renders the claim indefinite and ambiguous because it is not clear how the tissue protective cytokine could effect bone marrow if it is being used on cell, tissue or organ that is isolated from a mammalian body, that is, the method is directed to ex vivo exposure of the cell, tissue or organ to the cytokine. If the cell, tissue or organ to be protected is isolated from the body, how would the cytokine even interact with bone marrow? Moreover, if the tissue protected *is* bone marrow tissue, then the claim is even less clear, because how could a cytokine protect or maintain bone marrow if it does not "effect bone marrow"? Furthermore, it unclear what the term "effect" means in this

instance, that is, in what manner does the tissue protective cytokine "effect" bone marrow? Is the "effect" positive, as in stimulation of the tissue, or negative, as in suppressing the activity of the tissue, etc.? The metes and bounds of the claim thus cannot be ascertained.

21. Claims 54-58 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a conclusion step indicating that exposure to or administration of the tissue protective cytokine resulted in protection, maintenance or enhancement of viability (as in claims 54-56) or protection against tissue injury, etc. (as in claims 57-58).

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/24160 by Boissel et al., published 27 October 1994.

The claims are drawn to a method of protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing

said cell, tissue or organ to a pharmaceutical composition comprising a mutein recombinant tissue protective cytokine, wherein the protection does not effect bone marrow (claim 55), and wherein the recombinant cytokine lacks at least one erythropoietic activity (claim 56).

Boissel et al. teach mutein recombinant erythropoietin (EPO) molecules and therapeutic use of these molecules (see Abstract). The mutein EPO proteins are disclosed to have one or more amino acid modifications, such as substitution of particular amino acid residues (see pp. 22-23). For example, Boissel teaches EPO molecules with either enhanced or reduced biological activity (see Example II, p. 43). Mammalian-derived EPO-dependent cell lines are disclosed as being useful for such assays (see p. 31). Bioactivity assessment involves exposure of cells to recombinant EPO, and was measured as the ability to sustain cellular proliferation of the EPO-dependent cell line HCD57, which are a type of erythroid cell (see p. 33, lines 16-21). It is noted that neither claims 54 nor 55 recite that the tissue protective cytokine lacks any particular activity, only that the protection it provides "does not effect bone marrow." Additionally, none of the claims are limited to a particular type of cell, tissue or organ that is to be exposed to the recombinant tissue cytokine. Boissel teaches assessment of the mutein EPO proteins using bioassays such as Example II on p. 43, and discloses a bioassay using EPO-dependent mouse and human cell lines to evaluate the biological activity of particular mutein recombinant EPO molecules. Exposure of the cells to the mutein recombinant EPO would be expected to inherently result in their protection, maintenance or enhance their viability. Because there would be no bone marrow in

such isolated cell cultures, the protection would not affect bone marrow. Further, Boissel discloses that particular modified EPO muteins, in particular Δ48-52, had markedly decreased biological activity (see p. 48, lines 16-17), which would address the activity limitation of instant claim 56. Accordingly, the teachings of Boissel et al. anticipate instant claims 54-56.

24. Claims 57-58 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 6,153,407 to Sytkowski et al, issued November 28, 2000, listed on Applicant's IDS.

Sytkowski et al. teach the production and therapeutic use of erythropoietin proteins which have at least one amino acid residue in Domain 1 which differs from the amino acid residue in the corresponding position of wildtype erythropoietin and which has altered ability to regulate the growth and differentiation of red blood cell progenitors (see column 2, lines 36-41). Sytkowski discloses that Domain 1 refers to the amino acids which correspond to amino acids 99-110 of wildtype recombinant erythropoietin (see column 2, lines 41-44). Further, Sytkowski teaches that such modified recombinant mutant erythropoietin has decreased biological activity relative to wildtype erythropoietin protein, such as the ability to regulate growth and differentiation of red blood cell progenitor cells (see column 2, lines 63-65 and column 3, lines 63-65), which would anticipate the instantly claimed tissue protective cytokine "that lacks at least one activity selected from the group consisting of increasing hematocrit, vasoactive action, hyperactivating platelets, pro-coagulant activity and increasing production of

thrombocytes". The Examiner notes that the instant SEQ ID NO: 62 has a Ser→Glu substitution at residue 100 of wildtype recombinant erythropoietin (EPO). Thus, Sytkowski teaches the mutein recombinant EPO of instant SEQ ID NO: 2, with disclosed decreased erythropoietic activity relative to wildtype EPO. Sytkowski teaches that such modified EPO proteins with altered regulating ability can be used for therapeutic purposes, and that pharmaceutical compositions comprising an effective amount of the modified human recombinant EPO may be used in these methods (see column 4, lines 34-36 and 61-64). Sytkowski discloses administration to "patients" and "individuals" (see, for example, columns 19-21), which are generally accepted to mean humans, and thus would address the limitation of "mammal" in the instant claims. Accordingly, administration of an effective amount of the modified recombinant EPO protein with decreased erythropoietin activity to an individual would inherently result in the claimed protection of tissue injury and/or the restoration of tissue function, etc., regardless of the cause of tissue injury. Accordingly, the US patent by Sytkowski et al. anticipates instant claims 57-58.

Conclusion

25. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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February 16, 2007

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PRIMARY EXAMINER